REMARKS

An amendment to the specification is included to insert a benefit claim. Upon entry of the above amendment, claims 9, 11-17 and 21-58 will be pending. Claims 9, 13, 15, and 21-25 are amended, new claims 26-58 are added, and claims 18-20 are canceled by the amendment. Support for the amendments to the claims and for the new claims can be found throughout the specification. For example, support for amended claim 9 can be found, *e.g.*, at page 2, lines 9-10, and page 3, lines 30-31. Support for amended claim 13 can be found, *e.g.*, at page 4, line 1. Support for amended claim 15 can be found, *e.g.*, at page 2, lines 28-30, and at page 5, lines 21-23. Support for amended claims 21-25 can be found, *e.g.*, at page 4, lines 4-10 and 20-21, and at page 6, lines 22-23. Support for new claim 26 can be found, *e.g.*, at page 11, lines 3-6. Support for new claims 27, 28, 42, 43, and 47 can be found, *e.g.*, at page 5, lines 1-7. Support for new claims 29-32, 48, 49, and 52 can be found, *e.g.*, at page 6, lines 1-12. Further support for new claim 52 can be found, *e.g.*, at page 3, lines 12-17, and page 4, lines 1 and 2. Support for new claims 33-36 can be found, *e.g.*, at page 5, lines 1-7. Support for new claims 37-40 and 44-46 can be found, *e.g.*, at page 4, lines 24-28. Support for new claim 41 can be found, *e.g.*, at page 4, lines 4-7, and at page 6, lines 21-22. Support for new claims 50 and 54 can be found, *e.g.*, at page 2, lines 9-10. Support for new claims 51 and 55 can be found, *e.g.*, at page 11, lines 8-9. Support for new claim 53 can be found, *e.g.*, at page 4, lines 24-28. Support for new claims 56, 57 and 58 can be found, *e.g.*, page 4, lines 4-7 and 20-21, and page 5, lines 1-7. No new matter has been added.

Applicants thank the Examiner and her supervisor for granting an interview with the undersigned and her colleague, Allyson Hatton, Ph.D., on August 23, 2005. During the interview, several of the above proposed amendments and the presently submitted evidence were discussed. The Examiner indicated that the evidence of synergistic results could well support allowable claims of scope to be determined, but no agreement was reached.

The present claims are drawn to methods of treating chronic pulmonary obstructive disease (COPD). Prior to addressing the currently imposed ground for rejection, Applicants

believe it may be useful to explain some of the characteristics of this disease. COPD is a chronic and progressive disease of the airways typically seen in long-term cigarette smokers. It involves both emphysema (a lung condition in which the air sacs are permanently damaged, leading to loss of lung surface and elasticity, thereby impairing the gas exchange capacity of the lungs and the patient's ability to exhale) and chronic bronchitis (a persistent inflammation of the air passages characterized by excessive production of mucus). COPD patients exhibit chronic symptoms such as cough, shortness of breath ("dyspnea"), chest tightening, excessive sputum, wheezing, and impaired physical capacity. A common measure of the severity of the disease is the patient's "forced expiratory volume in one second," or FEV1, often expressed in comparison with the FEV1 that would be predicted for a healthy person of the same age and size. FEV1 is determined by measuring the volume of air that the patient can forcibly exhale in one second. A COPD patient having FEV1 $\geq$ 80% of predicted FEV1 is categorized as having mild COPD, while a patient having 50 % $\leq$ FEV1$<$ 80 % of predicted FEV1 is categorized as having moderate COPD, and a patient having 30 % $\leq$ FEV1 $<$ 50 % of predicted FEV1 is categorized as having severe COPD. A patient whose FEV1 is $<$ 30 % predicted, or $<$50% predicted and accompanied by chronic respiratory failure, is categorized as having very severe COPD (GOLD Guidelines 2004, p. 7, Figure 1-2; attached with the IDS and PTO-1449 submitted herewith). This chronic impairment in lung function worsens over time, and can be increasingly debilitating, leaving the patient less and less able to carry out a normal daily routine. In addition, the more severely affected patients occasionally experience acute exacerbations of their COPD symptoms in which their clinical status deteriorates markedly over a short time (typically 10-15 days), to the point that they become bedridden or even require hospitalization. Repeated exacerbations will accelerate the decline in lung function and health status. These crisis episodes cause extreme distress to the patient (the exacerbation episodes have been likened to a feeling of "drowning"), and can be fatal. In fact, COPD is currently ranked as the fourth most common cause of death throughout the world.

Applicants have unexpectedly found that treating a COPD patient with a combination of formoterol (or a salt or solvate thereof, or a solvate of such a salt) plus budesonide can reduce the

frequency and/or intensity of exacerbations, as well as improve the patient's lung function (measured by FEV1) more effectively than either of the agents alone. This represents a dramatic step forward in the treatment of this difficult disease.

Applicants note that the obviousness rejection with respect to Andersson *et al.* (U.S. Patent No. 6,598,603 B1) has been withdrawn. The claims now are rejected under 35 U.S.C. §103(a) as being obvious over Carling *et al.* (WO 93/11773) in view of Cazzola *et al.* (Ref. U) and Renkema *et al.* (*Chest* 109:1156-1162, 1996), and further in view of Giardina *et al.* (U.S. Patent No. 6,227,862 B1). The Examiner alleges that while Carling *et al.* do not expressly teach the treatment of COPD, Cazzola *et al.* teaches that formoterol is effective in patients with COPD, Renkema *et al.* teaches that treatment with corticosteroid (*i.e.*, budesonide) significantly reduced pulmonary symptoms in patients with COPD, and Giardina *et al.* report that COPD and asthma are respiratory diseases. The Examiner concludes that it would have been obvious to the skilled artisan to employ Carling's medicament to treat COPD "since COPD is well known respiratory disease as disclosed by Giardina *et al.*" (Office action at page 4). The Examiner further opines that each of the active agents (budesonide and formoterol) utilized in Carling's medicament is individually known to treat COPD conditions as taught by Cazzola *et al.* and Renkema *et al.*

Applicants traverse this rejection on a number of grounds:

1. The references do not provide either the motivation or the expectation of success necessary to make out a *prima facie* case of obviousness.

2. The prior art as a whole actually taught away from the claimed methods.

3. The surprising results observed by Applicants are cogent, objective evidence that the claimed methods cannot be deemed obvious.

4. Even years after the present application's filing date, experts in the field of respiratory therapy continued to express doubt that budesonide (whether alone or in the claimed combination therapy) would be useful for treating COPD.

These grounds are explained in detail below. As an initial matter, however, Applicants note that claim 9 has been amended to make the differences between the claimed invention and the teachings of the art even more pointed. As amended, claim 9 specifies that the claimed method

is effective to reduce the frequency and/or intensity of exacerbations in a patient suffering from COPD. Nothing in the art would have led one to expect that treatment with budesonide and formoterol would accomplish this important goal. An elaboration of this point is incorporated into the discussion below.

The primary reference is Carling, cited for its disclosure of use of a budesonide/ formoterol combination for treatment of what Carling describes as "respiratory disorders such as asthma" (page 1, lines 12-13). The Examiner acknowledges that Carling did not mention treatment of COPD in particular, but argues that since COPD is known to be a respiratory disorder (citing Giardina *et al.*), one of ordinary skill would have interpreted Carling's mention of "respiratory disorders" to encompass COPD (Office action at page 6). Since there is no more reason to read Carling's term as encompassing COPD than as encompassing any other randomly selected respiratory disorder, the Office action is essentially saying that Carling teaches use of the budesonide/formoterol composition for treatment of all conditions that have ever been classified as "respiratory disorders." This cannot be a reasonable interpretation of Carling. In view of the wide variety of unrelated conditions that can be classified as respiratory disorders (including, for example, cough, pulmonary hypertension, lung cancer, and tuberculosis, as well as asthma and COPD), reading Carling as teaching that one mode of treatment will work for all respiratory disorders is contrary to common sense. Applicants have previously presented evidence that those of skill in the art understand asthma and COPD to be fundamentally different diseases, with different causes and different treatments. Some of that evidence is again presented for the Examiner's reconsideration. For example, the Merck Manual reports that "[b]ecause of the clear differences between asthma and COPD, diagnosable asthma is not included with COPD" (17th Edition, 1999, at page 569). Table 68-6 in the Merck Manual (page 570) further refers to histological differences in asthma and COPD: eosinophil levels are increased in asthma patients but are normal in COPD patients; neutrophil levels are normal in asthmatics, but increased in COPD patients; the CD4:CD8 ratio is 4:1 in asthmatics, but is 1:4 in COPD patients; and gene expression of interleukins IL-4 and IL-5 is increased in asthmatics but is not increased in COPD patients. Furthermore, the editorial by K.F. Rabe (*Eur. Respir. J.* 22:874, 2003; of

record in the Information Disclosure Statement filed March 1, 2004) shows that, *even in 2003, long after the present application's priority date,* an expert in the field of respiratory disease repeatedly asserted that COPD and asthma are fundamentally different diseases that are unlikely to be successfully treated the same way. At page 874, left col., the author noted "We have all witnessed the heated discussions around inhaled steroids in COPD and have seen and read the data that confirm that asthma and COPD are completely different diseases, clinically and biologically....[Were] we all wrong, does this mean we no longer need to differentiate between asthma and COPD since the treatment will be the same in the end?" Dr. Rabe later emphasizes that "these two diseases...are fundamentally different in the vast majority of patients" (page 875, left column, emphasis added). Applicants simply do not see how this clear expression of how the art actually viewed the distinction between asthma and COPD can be ignored in interpreting what Carling meant by "respiratory diseases such as asthma." Rather than reading Carling's use of this phrase in a nonsensical way to sweep in all respiratory diseases, even those quite different from asthma, Applicants urge the Examiner to interpret it as it would have been read in context by one of ordinary skill: *i.e.*, to encompass disorders that are bronchospastic in nature, similar to asthma.

Similar arguments were made in Applicants' reply filed December 20, 2004. That reply pointed to a declaration of one of the Carling *et al.* inventors (Declaration of Jan Trofast filed March 1, 2004; the "2004 Trofast Declaration") as further evidence that the term "respiratory disorders," as it is used in the Carling *et al.* reference, must be interpreted in context. In response, the present Office action merely reiterates that, because Giardina *et al.* (a reference with no relevance to the presently claimed invention) classified COPD as a "respiratory disorder," the 2004 Trofast Declaration was "not persuasive." Applicants maintain that one must interpret the language of the Carling reference in a way that is internally consistent, and not distort it beyond what Carling could possibly have meant, simply to serve the interest of making out the elements of an obviousness rejection. The 2004 Trofast Declaration makes it clear that, in the context of the Carling reference, the term "respiratory disorders" means not ALL respiratory disorders, but rather those respiratory disorders similar to asthma, *i.e.*, mainly of

bronchospastic nature. This would not include COPD. This is entirely consistent with the other evidence of record. The Examiner has offered no reason to justify an interpretation broader than Applicants', other than the fact that a broader interpretation can be found in an unrelated reference on a completely different topic.

In further support of the rejection, the Examiner argues that Cazzola *et al.* teaches that formoterol alone "is effective in patients with COPD" and that Renkema teaches that budesonide alone "significantly reduced pulmonary symptoms in COPD patients." Renkema did test whether relatively high doses of budesonide (1600 µg per day) had value in treating COPD over a two-year period, noting that previous short-term studies had shown budesonide to have "little or no effect" (page 1156, col. 1). Renkema reported that, while certain subjective "symptom scores"[1] did decrease during long-term treatment with budesonide alone, neither airflow obstruction (as measured by FEV1) nor the frequency or duration of exacerbations was affected by treatment with budesonide (Renkema *et al.*, p. 1160, column 1). This lack of effect on exacerbations is particularly significant in view of the present amendment to claim 9. None of the other cited references even mentions exacerbations. Cazzola *et al.* focused solely on airflow obstruction (measuring FEV1), not exacerbations, in their formoterol study subjects. Carling, as discussed above, was concerned solely with asthma and asthma-like disorders, so had no reason to look at COPD exacerbations, and indeed did not. Giardina is simply irrelevant. Given that there was no reason to expect that either budesonide alone or formoterol alone would be effective in reducing the frequency or intensity of COPD exacerbations, one of ordinary skill would not have been motivated to try them in combination for this purpose, as required by amended claim 9—and certainly would not have had any reasonable expectation of success even if the experiment had been attempted. In view of the above, Applicants submit that claim 9 and

[1] The symptom score is described at the top of the second column on page 1157: "Patients were asked to rate the severity of dyspnea (scale, 0 to 5), dyspnea on exertion (scale, 0 to 3), early morning dyspnea (scale, 0 to 3), cough (scale, 0 to 3) and wheeze (scale, 0 to 3). A score of 0 was given if the complaint was absent; a higher value corresponded with increasing severity. A total complaint score (scale, 0 to 17) was calculated by adding up the scores from each question." Dyspnea is difficult or labored breathing. The "symptom score" is thus derived from the patient's own subjective characterization of his difficulty in breathing, rather than on an objectively quantifiable measure such as FEV1 or number of hospitalizations for exacerbations.

all claims dependent thereon (*i.e.*, claims 11-17 and 21-40) are patentable over the cited art. Withdrawal of the rejection on that basis is respectfully requested.

Furthermore, Applicants note that the art, taken as a whole, actually *taught away* from any use of budesonide (alone or in combination with another drug) to treat COPD. This can be seen from a careful consideration of what the art of record actually teaches. First, it is well established that short-term use of budesonide alone (at any dosage) has no demonstrable benefit in treating COPD. Renkema himself notes this in the first paragraph on page 1156. **Thus, the art teaches away from such short-term use.** Second, Renkema's long-term trials of budesonide treatment, which employed a relatively high dose of 1600 μg budesonide per day, demonstrated what Renkema characterized as "limited" beneficial effects in COPD patients (page 1161, col. 2, last paragraph). Renkema's modest results rule out any reason to attempt long-term trials with lower doses of budesonide; indeed, Renkema himself states, "It may be that still higher doses of corticosteroids are needed in patients with COPD" (page 1161, col. 2, second paragraph). This can be taken as a teaching-away from use of anything less than 1600 μg budesonide per day. However, other art of record makes it clear that even 1600 μg is a dangerously high long-term daily dose of budesonide. *Nederlands Tijdschrift voor Geneeskunde* (vol. 140:94-98, 1996) reports that 800-1600 μg budesonide per day is associated with an unexpectedly high rate of opportunistic lung infections in COPD patients. According to this reference,

> Inhalation corticosteroids are of great importance in the treatment of asthmatic patients. Their place in the treatment of patients with COPD is much less clear....The high dosages of inhalation corticosteroids may have been involved in the cause of these infections by suppressing the T-cell response locally. In view of this, longterm inhalation corticosteroid treatment should be prescribed in COPD patients only if the efficacy of the medication has been proved in the individual patient involved.

This teaching that inhaled corticosteroids are both risky and of uncertain benefit in COPD patients and long term inhaled corticosteroid treatment should be prescribed only in limited situations **is plainly a teaching-away from long term treatment of COPD patients with high doses of corticosteroids in general, and budesonide in particular.** This teaching-away tempers any reading of Renkema that high-dose budesonide has possible benefits in COPD. One

of ordinary skill in the art, reading both Renkema and Nederlands Tijdschrift voor Geneeskunde, would come away with the understanding that (1) if budesonide has any role in treatment of COPD, it would be only if it were used in large doses (at least 1600 μg per day) over a long term, but (2) unfortunately such use would carry a risk of pulmonary infection due to immunosuppression that in most cases would outweigh any benefit to the patient. There is certainly no incentive derivable from these references to investigate use in COPD patients of a combination treatment involving budesonide and a second active ingredient, particularly since such combination treatment would make it unclear what benefits (if any) the patient might be deriving from the budesonide part of the combination to counterbalance the very real risks of taking large doses of corticosteroids long term. **In sum, the art teaches away from use of budesonide (either alone or in combination with a second active ingredient) for the short- or long-term treatment of COPD, whether at low doses (which Renkema suggests won't be of any value) or high (which Nederlands Tijdschrift voor Geneeskunde teaches increase the risk of infections while providing no clear benefit).**

As still another basis for withdrawal of the rejection of claim 9 and its dependents, Applicants remind the Examiner that extensive evidence of surprising results is already of record in this case, evidence that the Examiner persists in dismissing because "Applicants' claims are not drawn to alleged synergism." (Office action at page 7.) It is unclear what is meant by this statement. U.S. law does not require that claims be "drawn to synergism" in order for surprising results to be taken as conclusive evidence of nonobviousness. See, for example, Knoll Pharmaceutical Company, Inc. v. Teva Pharmaceuticals USA, Inc., 367 F.3d 1381 (Fed. Cir. 2004) and In re Chu, 66 F.3d 292 (Fed. Cir. 1995), where the court held that evidence of surprising results must be considered and can be dispositive of nonobviousness even if the evidence is not disclosed in the specification as filed. (If the evidence need not be in the specification as filed, it certainly need not be recited in the claims.) Applicants have provided ample evidence of surprising results sufficient to remove any doubt as to the nonobviousness of the claimed methods, even prior to the present amendment regarding reducing the frequency and/or intensity of exacerbations. This evidence was submitted long ago (April 25, 2002, and

December 13, 2002) in declarations describing the results of clinical trials demonstrating unexpectedly better results with the presently claimed combination treatment, compared to treatment with either budesonide or formoterol alone. In the Interview, Applicants provided several graphs illustrating evidence of synergistic results with the claimed combination therapy. Some of these graphs had been previously submitted; others were new. For the Examiner's convenience, the graphs shown in the Interview are collected in and explained by the new Declaration of Jan Trofast (the "2005 Trofast Declaration") submitted herewith. Two of the graphs (submitted as Appendices 1 and 4) are not identical to those shown in the interview, but illustrate the same subject matter. The data in these two graphs represent a revised statistical analysis, and the results are consistent with the results shown previously.

Applicants briefly summarize the graphs here. The Examiner is urged to review the declaration and Calverley *et al.*, *Eur. Resp. J.* 22:912-919, 2003 (cited in the PTO Form 1499 submitted March 1, 2004), to see a fuller description of the data.

The graphs submitted as Appendices 1-9 with the attached declaration illustrate data collected from a placebo-controlled 12-month clinical trial that was performed using a combination of budesonide/formoterol fumarate dihydrate (under the product name Symbicort®) in the treatment of moderate to severe COPD (formoterol is the biologically active moiety in formoterol fumarate dihydrate (FFD)). In summary, before randomization, 1022 patients were treated in a 2 week initial run-in period with oral prednisolone (30 mg once daily), inhaled FFD (Oxis®; 2 puffs twice per day, each puff delivering 4.5 μg FFD to the patient from a metered dose[2] of 6.0 μg FFD), and terbutaline as needed (Bricanyl®; 0.5 mg by inhalation). The patients had the following profile:

Age ≥ 40 years

COPD diagnosis since at least 2 years prior to the study

[2] A "metered dose" is the amount of product that is positioned in the inhaler for delivery to the patient with each puff. Not all of the metered dose is delivered to the patient; some product will stick to the sides of the inhaler, or will otherwise remain in the inhaler. A "delivered dose" is the amount of product that exits the inhaler. This amount is less than the metered dose.

At least 10 pack years smoking history[3]

Documented use of inhaled bronchodilators as a quick relief medicine

At least one severe COPD exacerbation within 2-12 months of entry

$FEV_1 \leq 50\%$ predicted normal, pre-bronchodilator

$FEV_1/VC \leq 70\%$ pre-bronchodilator

(FEV_1 = Forced Expiratory Volume within 1 second, VC = vital capacity)

All of the following medications and the placebo were delivered from a Turbuhaler® inhaler. The patients were randomized into four groups and treated as follows:

Group 1: Budesonide/FFD combination (Symbicort®; 2 puffs twice per day, each puff delivering 160 μg budesonide/4.5 μg FFD to the patient (corresponding to a metered dose of 200 μg budesonide and 6.0 μg FFD for the monoproducts))

Group 2: Budesonide alone (Pulmicort®; 2 puffs twice per day, each puff delivering 160 μg budesonide to the patient from a metered dose of 200 μg budesonide)

Group 3: FFD alone (Oxis®; 2 puffs twice per day, each puff delivering 4.5 μg FFD to the patient from a metered dose of 6.0 μg FFD)

Group 4: Inhaled placebo composition (2 puffs, twice daily, no active ingredients)

The patients were studied for 12 months, with various measures of COPD symptoms being regularly recorded. The results of this study suggest that the combination of budesonide and FFD (*i.e.*, formoterol) produces several synergistic effects. For example, as shown in the graph titled "Symbicort reduces the risk of first exacerbation requiring medical intervention"[4] (Appendix 1), the hazard rate was reduced (compared to placebo) by **28.5 %** in patients treated with the budesonide/FFD combination. The corresponding reduction for patients treated with budesonide alone was **7.5 %,** while FFD alone actually produced an increase (compared to

[3] As understood in the art, "10 pack years" indicates that the individual smoked a pack a day for 10 years, or 2 packs a day for 5 years, etc.

[4] Severe exacerbations were considered to be exacerbations requiring medical intervention, *i.e.*, administration of antibiotics and/or oral steroids, and/or hospitalization due to respiratory symptoms.

placebo) of **1.5 %**. A merely additive effect would have produced a 6.0 % reduction[5]. Thus, it is clear that the combination product produced a synergistic effect.

The graph titled "Symbicort reduces the number of severe exacerbations/patient/year" (Appendix 2) also strongly implies a synergistic effect of the budesonide/FFD combination therapy. As compared to treatment with placebo, treatment with FFD alone actually increased the number of exacerbations per patient per year slightly (**+3%**), while treatment with budesonide alone decreased the number of exacerbations per patient per year by **12%**. **Patients treated with the budesonide/FFD combination, however, exhibited a 24% reduction in exacerbations.** This result demonstrates a synergistic effect, as the 24% reduction is much greater than the 9% reduction expected if the effect of the combination therapy were merely additive.

A synergistic effect was also indicated in the patients' need for oral steroids during the course of the study, as shown in the graph titled "Symbicort reduces need for oral steroids" (Appendix 3). Treatment with budesonide alone reduced the hazard rate of time to first oral steroid use by **14%** compared to placebo, and treatment with FFD alone reduced the hazard rate by **13%** as compared to placebo. **In contrast, treatment with the budesonide/FFD combination reduced the hazard rate of time to first oral steroid by 42.3% versus placebo.** This is far better than the 27% reduction that would have been expected from an additive effect of the individual budesonide and FFD components.

A synergistic effect was also observed in the effect on night awakenings, as shown in the graph titled "Symbicort increases nights without awakenings" (Appendix 4). Treatment with either budesonide alone or FFD alone resulted in an adjusted mean change in awakenings-free nights of **+3.7 %** (compared to placebo). If budesonide and FFD in combination had a merely additive effect on the change in awakenings-free nights, the adjusted mean change of the

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[5] In order to assure the stability of the first order approximation used above to assess the additive effects, a fully elaborated approach is also presented. By treating these data in a multiplicative way (the model being relative), the additive effect of budesonide and formoterol is = 100 – (100-7.5)*(100+1.5)/100 = 6.1 % and the combination (Symbicort®) over this is = 100 - 100*100*(100-28.5)/((100-7.5)*(100+1.5)) = 23.8 %. Note that this effect is even greater than suggested above (= 28.5-6.0 = 22.5 %), showing that calculation on the additive scale gives a conservative estimate.

combination therapy (compared to placebo) would be expected to be **+7.4 %.** However, treatment with the combination therapy resulted in an adjusted mean change in awakenings-free nights (compared to placebo) of **+ 9.2 %,** much greater than the calculated additive effect of 7.4 %.

A synergistic effect was also indicated in the morning peak expiratory flow (PEF), as shown in the graph titled "Symbicort rapidly improves and maintains morning PEF" (Appendix 5). The difference in adjusted mean change of morning PEF, as compared to placebo, was **3.5** L/min for the patients treated with budesonide alone, **11.1** L/min for those treated with FFD alone, **and 18.3 L/min for the patients treated with the budesonide/FFD combination,** *i.e.*, 3.7 L/min higher than would be expected if the effect were merely additive. These data were presented previously in the declaration of Christer Hultquist, filed December 13, 2002, and supplement the data presented in Calverley *et al.* at page 915, column 2 and in Figure 3(a) at page 916.

The graph titled "Symbicort rapidly improves and maintains evening PEF" (Appendix 6) strongly implies a synergistic effect on the patients' evening peak expiratory volume (PEF). The difference in adjusted mean change of evening PEF, as compared to the placebo, was **2.0** L/min for the patients treated with budesonide alone, **8.9** L/min for those treated with FFD alone, and **14.1 L/min for the patients treated with the budesonide/FFD combination,** *i.e.,* 3.2 L/min higher than would be expected if the effect of the budesonide/FFD combination were merely additive.

The graph titled "Symbicort produces rapid and maintained improvement in lung function (FEV1)" (Appendix 7) illustrates that FEV1 decline was less severe in patients treated with a budesonide/FFD combination therapy than in those treated with either monotherapy. The combination therapy was **14%** better than placebo in this regard while the monotherapies were only **8%** and **2%** better than placebo. Also, as illustrated by the graph titled "Symbicort improves health related quality of life, HRQL" (Appendix 8), the mean change in total score on St. George's Respiratory Questionnaire (SGRQ) as compared to placebo was **-7.5**, which was a

greater improvement than that observed following treatment with budesonide alone (**-3.0**) or FFD alone (**-4.1**)[6].

Finally, as illustrated by the graph titled "Symbicort reduces discontinuations compared to other treatments" (Appendix 9), fewer patients withdrew from the study when they received the budesonide/FFD combination therapy than when they received either of the monotherapies. These data supplement the data in Table 1 of Calverley *et al.* at page 914, which reports that **71%** of the patients originally enrolled in the study and who received treatment with the combination of budesonide and FFD completed the study. By comparison, only **59%** of patients receiving placebo completed the study, approximately the same as those receiving FFD alone (**56%**) or budesonide alone (**60%**). The multiple beneficial effects described above may have contributed to the fact that fewer patients receiving the budesonide/FFD combination therapy withdrew from the study.

Applicants ask the Examiner to reconsider the above clinical evidence as proof that the presently claimed methods produce results that could not have been predicted from anything in the art. Under U.S. law, the Examiner must take into account any objective indicia of non-obviousness, such as surprising results, when considering whether the claims are obvious over prior art.

As a final ground for establishing the nonobviousness of the claimed methods, Applicants remind the Examiner of substantial evidence of record concerning skepticism of experts, one of the standard objective indicia of nonobviousness recognized under U.S. law (see, *e.g.*, Graham v. John Deere, 383 U.S. 1 (1966)). For example, the above-cited editorial by K.F. Rabe shows that though this expert was "happy to adopt" use of formoterol/budesonide combination therapy for treatment of asthma, **he was skeptical that the combination could be generally useful in treatment of COPD**—and this was in 2003, following publication of two clinical trials disclosing the benefits of the combination therapy in COPD. Another post-filing date article (Vestbo et *al.*, *Lancet* 353:1819, 1999; of record in the Information Disclosure Statement filed herewith) flatly states in the abstract, **"Inhaled budesonide was of no clinical benefit in COPD**

[6] A change of *minus* 4 points in the SGRQ represents a clinically important improvement in health related quality of life. The more negative the score, the better the quality of life.

patients recruited from the general population by screening. We question the role of long-term inhaled corticosteroids in the treatment of mild to moderate COPD." It is clear from such post-filing date evidence that the art was skeptical that budesonide alone or in the claimed combination therapy was of any value in treating COPD, even years after Applicants' priority date.

In summary, Applicants have established

- that the cited art provided neither motivation to carry out the claimed methods, nor expectation of success upon doing so;
- that the art actually taught away from the claimed methods;
- that administration of the claimed combination produces surprisingly synergistic results; and
- that the bias in the art against the usefulness of inhaled corticosteroids in treating COPD was so pronounced that it remained even years after Applicants' filing date.

Any one of these points would be sufficient to mandate withdrawal of the rejection. Such action is respectfully requested.

Applicants note that the present amendment adds new independent claims 41, 52 and 56-58 and a number of claims dependent from claims 41 and 52. As discussed below, each of these claims is plainly patentable over the cited references.

New claim 41 is drawn to a method of treating a patient suffering from COPD with (i) a daily dose of 2 to 120 nmol of formoterol (or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt); and (ii) a daily dose of 45 to 2200 μg of budesonide, wherein the two active ingredients are optionally in admixture, and wherein the daily dose of each active ingredient is administered in one to four divided doses per day. New claim 52 is drawn to a method of treating a patient suffering from COPD by administering, via inhalation from a pressurized metered dose inhaler, a composition including formoterol (or a salt or solvate or solvate of such a salt), budesonide, and propellant P227, wherein the molar ratio of the active ingredients is as specified in the claim. As elaborated below, there are at least three separate

grounds for concluding that none of the cited references, even in combination, renders either of these new independent claims obvious.

First, Applicants point out that the surprising results alluded to above with respect to claim 9 apply equally to claims 41, 52 and 56-58. The art gave no reason whatsoever to expect the synergistic results of the presently claimed combination therapy. That alone is sufficient evidence to establish the nonobviousness of claims 41, 52 and 56-58.

Second, Applicants refer the Examiner again to the teachings-away in the art, as described above. One of ordinary skill would understand from the art that budesonide was not a potentially useful treatment for COPD, based on teachings in the art that (1) short-term therapy with budesonide has no demonstrable benefit; (2) there is no evidence that budesonide has any efficacy at all at moderate or low doses; (3) even at a high dose, long-term therapy with budesonide showed very modest benefit; and (4) long-term therapy with high doses of budesonide is known to be associated with an increased risk of pulmonary infection. This combination of teachings in the art would have convinced one of ordinary skill in 1997 that there was no established overall benefit to using budesonide at any dosage level for treatment of COPD sufficient to counterbalance the risk. Even if one thought to do further experiments with budesonide in order to sort out the relative risks/benefits of budesonide treatment in COPD, a person of ordinary skill at the instant priority date would realize that the experiments should *not* be done with a combination therapy (such as the claimed method) that would make it impossible to determine what positive or negative effects are attributable to budesonide itself. Thus, the art, taken as a whole, would have dissuaded one of ordinary skill from even trying the methods of claims 41, 52, 56-58, or any claim that depends therefrom.

Third, Applicants point out that there are a number of dependent claims in this application, including several added by the present amendment. Each provides additional limitations that constitute further distinctions over the cited art. For example, claims 28, 34, 47, and 58 specify that the amount of budesonide administered is 160 to 640 μg per day (1 to 4 unit doses at 160 μg per unit dose). Claims 36 and 43 specify that the amount is 320 to 640 μg per day (1 or 2 unit doses at 320 μg per unit dose). Claims 38 and 44 specify that the amount is 80

to 320 μg per day (1 to 4 unit doses at 80 μg per unit dose). Claims 40 and 46 specify that the amount is 160 to 320 μg per day (1 or 2 unit doses at 160 μg per unit dose). The Examiner has cited no art that would indicate any of these budesonide daily dosage ranges would have any value in treating COPD. Renkema taught that even a much higher dose of budesonide (1600 μg per day) provided only modest benefit and proposed that still higher doses should be tested, thereby profoundly teaching away from the relatively low dosage ranges in claims 28, 34, 36, 38, 40, 43, 44, 46, 47, and 58. The post-filing date clinical trial of budesonide alone reported by Vestbo *et al.* 1999 (discussed above) demonstrated that a daily dose of 1200 μg for six months followed by 800 μg daily for 30 months produced no clinical benefit in COPD patients, making the relatively low daily doses of budesonide (80 to 640 μg) for the combination therapy specified by the above claims even less obvious.

In view of the above, Applicants request that the rejection be withdrawn and the claims allowed.

Applicants request that the Examiner consider the references enclosed with the attached supplementary information disclosure statement and return an initialed copy of the Form PTO-1449. Applicants also repeat their request in the response filed December 20, 2004, that the Examiner consider the references cited in the Form PTO-1449 originally submitted with the application on November 13, 2001, and submitted a second time by facsimile on July 19, 2002. Examiner noted on a copy of the Form PTO-1449 returned to Applicants on January 29, 2002, that references AF-AQ were not provided. Applicants point out that reference AF was originally cited by the Examiner in the U.S. priority application 09/194,290 (hereafter, the "'290 application"), filed November 23, 1998, and reference AG was originally submitted by Applicants in the '290 application. Documents AH-AQ were originally submitted by Applicants in U.S. priority application 09/670,457, filed September 26, 2000. Thus, all of the references are of record in this case and presumably available to the Examiner. Applicants therefore request that the Examiner consider these references and return an initialed copy of the Form PTO-1449. *New copies of these references will be provided if necessary.*

Enclosed is a $1850 check for excess claim fees, a $1020 check for the fee for a Petition for Extension of Time for three months, and a $1370 check for the fee for a Petition to Accept an Unintentionally Delayed Benefit Claim. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-150003.

Respectfully submitted,

Date: Nov. 4, 2005

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